Brain morphometry in Tourette's syndrome: The influence of comorbid attention-deficit/hyperactivity disorder

Article abstract—Three separate groups, using MRI, have reported basal ganglia abnormalities in Tourette's syndrome (TS). We found similar abnormalities in boys with attention-deficit/hyperactivity disorder (ADHD). Because TS and ADHD are frequently comorbid, we contrasted ADHD boys with and without TS along with control subjects. As expected, we found a significant loss of the normal globus pallidus asymmetry in the patients, but presence or absence of TS did not differentiate the ADHD groups. We conclude that accounting for ADHD comorbidity will be important in future TS morphometric studies.

NEUROLOGY 1996;47:1581–1583

F.X. Castellanos, MD; J.N. Giedd, MD; S.D. Hamburger, MA, MS; W.L. Marsh, BA; and J.L. Rapoport, MD

Three independent groups reported abnormal basal ganglia asymmetries and volumes in Tourette's syndrome (TS) patients using MRI.[1-3] Patients with TS often have comorbid conditions, most commonly attention-deficit/hyperactivity disorder (ADHD), although the nature of this association remains unclear.[4,5] The morphometric study contrasting TS subjects with and without ADHD found TS patients without ADHD were no different from control subjects on any morphometric measure.[1] However, they did not include ADHD subjects without TS.

A study of MRI brain morphometry for 57 ADHD boys without TS and 55 matched control subjects found decreased normal asymmetry and reduced volumes in right anterior brain, right caudate, and right globus pallidus.[6,7] The similarities of findings across these studies and the known comorbidity of ADHD and TS motivated an examination of cerebrum, "anterior frontal," caudate, putamen, and globus pallidus volumes and asymmetries in 14 boys comorbid for ADHD and TS compared with 26 boys with ADHD without a tic disorder and 31 normal boys. We hypothesized that morphometric differences in comorbid patients might be accounted for by the presence of ADHD.

Methods. Healthy boys (n = 31, age 6.7 to 13.9 years) were recruited from the community and comprehensively screened for absence of psychopathology, as described elsewhere.[8]

Boys with ADHD without a tic disorder (ADHD alone) (n = 26, age 6.6 to 14.4 years) and probands comorbid for TS + ADHD (n = 14, age 7.1 to 13.8) were recruited for a double-blind stimulant trial described elsewhere.[7] The ADHD-alone patients and control subjects were selected from the larger samples reported elsewhere[6,7] to match the TS+ADHD patients in age, gender, and handedness. No subject had been previously treated with neuroleptics. Inclusion criteria were Conners Teacher Hyperactivity rating greater than 2 SD above age mean and DSM-III-R diagnosis of ADHD based on structured psychiatric interviews with a parent and the patient. The diagnosis of TS was established on the basis of confirmed observation of tics lasting longer than 1 year and by our own direct observations during controlled stimulant trials.

Consent from the child and written consent from parents were obtained. The NIMH Institutional Review Board approved the protocol.

All subjects were scanned on the same 1.5-T GE Signa scanner. T_1-weighted images with contiguous 1.5-mm sagittal slices and 2.0-mm coronal slices were obtained with echo time 5 ms, repetition time 24 ms, flip angle 45°, acquisition matrix 256 × 192, number of excitations = 1, and 24-cm field of view.

All raters were "blind" to subject characteristics. A semiautomated procedure was used to "remove" the brain from the intracranial cavity and quantify the cerebral hemispheres excluding cerebellum and brainstem from axial slices. This technique was validated by comparison with postmortem specimens and with volumes obtained from conventional slice-by-slice hand tracing (intraclass correlation [ICC] 0.95).[8]

We defined an "anterior frontal region" for each hemisphere as all brain matter anterior to a coronal plane intersecting the anterior-most point of the corpus callosum, excluding temporal lobe. This region overlaps primarily with prefrontal cortex but also includes subcortical white matter. Intrarater ICC for this semiautomated measure was 0.98.

Caudate (head and body) and putamen were manually outlined from every other coronal slice using public domain NIH Image (version 1.55).[9] Intrarater reliability was 0.89 for caudate and 0.85 for putamen. Globus pallidus, bounded medially by internal capsule and laterally by putamen, was measured on each coronal slice beginning 2 mm anterior to the anterior commissure and proceeding posteriorly for a total of 14 mm. Thus bounded, intrarater reliability was adequate (0.85). This measure does not distinguish internal and external segments. Further details are provided elsewhere.[7,8]

Statistical analysis. We performed ANCOVA using the BMDP package in SAS (version 6.07), with diagnosis as the between-groups factor and estimated Full-Scale IQ and total brain volume[7] as covariates for volumes and symmetry indexes. Symmetry was defined as $((R - L)/[(R + L) \cdot 0.5]) \cdot 100$. Because the patient groups differed significantly from control subjects in the proportion of strongly right-handed subjects, confirmatory analyses were performed excluding all subjects who were not strongly right-handed. Regions that exhibited significant group differences were tested with Duncan's post-hoc test to determine significant pair-wise differences at $\alpha = 0.05$.

Table 1 *Demographic data for ADHD boys with and without TS and control subjects*

	TS + ADHD	ADHD alone	Control boys	F	p*	Comment†
n	14	26	31			
Age in years (SD)	10.36 (1.9)	10.69 (1.9)	10.86 (2.1)	0.31	0.73	
Conners Hyperactivity Rating (0–3)	1.77 (0.7)	1.71 (0.8)	0.31 (0.5)	**37.80**	**.0001**	(TS = ADHD) > C
WISC-R Vocabulary Score	11.29 (3.0)	12.12 (3.5)	14.17 (2.9)	**5.09**	**.009**	(TS = ADHD) < C
WISC-R Block Design Score	10.29 (2.7)	12.60 (3.1)	14.03 (3.0)	**7.63**	**.001**	TS < (ADHD = C)
Estimated Full-Scale IQ‡	104.57 (13.0)	113.60 (17.0)	123.80 (13.9)	**8.48**	**.0005**	(TS = ADHD) < C
Number strongly right-handed (%)	10 (71.4)	20 (76.9)	29 (93.5)	**4.28**§	**.04**	(TS = ADHD) < C
Total brain volume (ml)	1118.46 (124.4)	1119.28 (124.7)	1172.78 (135.0)	1.51	.23	

* All probabilities are two-tailed. Statistically significant values in boldface. Values in parentheses represent standard deviation.
† Significant post-hoc pair-wise comparisons. TS = TS + ADHD; ADHD = ADHD alone; C = control boys.
‡ Derived from Vocabulary and Block Design scores. For details see reference 7.
§ Chi-square collapsed to 1 *df* due to small samples.

Table 2 *Adjusted* means (in ml) and asymmetry indices for ADHD boys with and without TS and control subjects*

	TS + ADHD		ADHD alone		Control boys		Asymmetry (%)†					
	R	L	R	L	R	L	TS	ADHD	C	F‡	p	Comment
Anterior frontal	88.77	85.36	81.69	79.95	86.50	77.40	6.11	2.68	10.81	1.65	0.20	
Caudate	4.90	4.88	5.19	5.12	5.10	4.98	0.16	1.41	2.46	0.63	0.53	
Putamen	5.50	5.71	5.36	5.56	5.36	5.60	−3.18	−3.44	−4.69	0.85	0.43	
Globus pallidus	1.19	1.21	1.13	1.14	1.22	1.16	−2.98	−1.16	6.52	**5.05**	**0.009**	(TS = ADHD) < C

* Adjusted for total brain volume and estimated full-scale IQ as described in reference 7. Abbreviations are the same as in table 1.
† Asymmetry index = ((Right − Left)/[(Right + Left) · 0.5]) · 100. A positive asymmetry index indicates right is greater than left.
‡ F ratio from ANCOVA for asymmetry indices.

Results. As table 1 demonstrates, the groups did not differ significantly in age. Both patient groups differed significantly from control subjects in hyperactivity, Wechsler Intelligence Scale for Children-Revised (WISC-R) Vocabulary IQ score, and estimated Full-Scale IQ but did not differ from each other. The WISC-R Block Design score of the comorbid group was significantly lower than both the ADHD-alone group and control subjects.

As shown in table 2, the only structure that was significantly different between groups on ANCOVA was the globus pallidus. The right > left asymmetry of the control group was reversed in both patient groups, which did not differ significantly from each other. We obtained the same result when we limited the analyses to strongly right-handed subjects (asymmetry $F = 4.06$, $(2,52)$, $p = 0.02$) or when right and left globus pallidus volumes were analyzed instead of asymmetry ratios (side by diagnosis $F = 3.15$, $(2,66)$, $p = 0.05$).

Discussion. Reports of reduced basal ganglia volumes and asymmetries in TS[1-3] are consistent with the prominent role in motor control imputed to these structures.[10] However, it may be too early to draw firm conclusions from this scant literature. For example, Peterson et al.[2] did not find any significant differences in their planned analyses of individual basal ganglia structures; they obtained significant results using measures that were constructed post-hoc. Singer et al.[1] found that TS-alone subjects did not differ significantly from control subjects on any measure. The report of Hyde et al.[3] of significant differences in anterior caudate between monozygotic twins discordant for tic severity is also confounded by the high proportion of subjects with ADHD (personal communication, Dr. T. Hyde, September 12, 1995).[3]

Our data suggest that TS + ADHD subjects, if studied in larger samples, might differ morphometrically from ADHD subjects who do not have TS. However, both patient groups showed a loss of normal globus pallidus asymmetry and did not differ significantly from each other. Future morphometric analyses of TS will need to account for psychiatric comorbidity, particularly for ADHD.

From the Child Psychiatry Branch, National Institute of Mental Health, Bethesda, MD.

Received November 30, 1995. Accepted in final form May 24, 1996.

Address correspondence and reprint requests to Dr. F.X. Castellanos, 10 Center Drive-Room 6N240, Bethesda, MD 20892-1600.

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Levodopa therapy improves motor function in HIV-infected children with extrapyramidal syndromes

Article abstract—Five children with human immunodeficiency virus type-1 (HIV-1) infection, aged 4 to 13 years, manifested extrapyramidal dysfunction characterized by rigidity/stiffness, ambulation difficulties/shuffling gait, dysarthria/drooling/swallowing dysfunction, hypomimetic/inexpressive facies, and bradykinesia. Levodopa therapy caused an initial improvement in all symptoms, and the effect was sustained in most patients. Levodopa is a useful adjunctive therapy in HIV-1–infected children with extrapyramidal syndromes, by enhancing motor function and improving their quality of life.

NEUROLOGY 1996;47:1583–1585

M. Mintz, MD; M. Tardieu, MD; L. Hoyt, MD; G. McSherry, MD; J. Mendelson, MD; and J. Oleske, MD

Human immunodeficiency virus type 1 (HIV-1) infection in the pediatric population is most often transmitted vertically (i.e., mother to child) in the United States and Europe.[1] However, there are subpopulations infected horizontally, particularly within the hemophiliac population.[2] Approximately 20% of perinatally infected children become symptomatic within the first 2 years, whereas others do not display significant symptoms of AIDS until much later; horizontally infected children tend to have a more latent course.[1-4]

HIV-1 infection of the CNS can cause a well-defined encephalopathy in children termed HIV-associated progressive encephalopathy (PE) and an analogous process in adults called AIDS dementia complex (ADC).[5] PE is a progressive neurologic deterioration, characterized by impairment of brain growth, cognitive decline defined by deteriorating performance on neuropsychometric tests, and a progressive motor dysfunction that often results in spasticity. Neuroradiologic and neuropathologic studies have provided confirmation of the clinical impressions, with diffuse cerebral parenchymal volume loss ("atrophy") and diminished brain weight; scattered cerebral vasculopathy with vascular mineralizations, particularly in the basal ganglia; reactive astrocytosis most evident within the white matter; glial/microglial nodules; and multinucleated giant cells.[6] Despite the extensive pathology in the basal ganglia and the possibility of dopaminergic dysfunction in PE/ADC, classic "parkinsonian"-like or rigid/dystonic syndromes are uncommon in pediatric AIDS.[7,8] We report five children with severe rigidity syndromes causing serious disability ameliorated by levodopa therapy.

Case reports. Patient 1 was a perinatally HIV-1–infected boy who presented at 5 years of age with the onset of a progressive motor deterioration and cerebral parenchymal volume loss on CT but without specific changes in the basal ganglia; he was diagnosed as PE. Additionally, the patient possessed severe immunodeficiency (absolute CD4 $< 50/\mu l$). The initial motor findings were predominantly characterized by a diffuse increase in extremity tone, pathologically increased deep tendon reflexes with sustained ankle clonus, a "stiff-legged," wide-based gait requiring support, dysarthria, and postural imbalance. Secondary to the PE and severe immunodeficiency, zidovudine (AZT) was instituted at a dose of 180 mg/m^2 every 6 hours and resulted in a dramatic neurologic improvement within 6 months, with a "re-expansion" of cerebral parenchymal volume on CT and resolving clinical neuromotor function with improved ambulation and articulation. After 1 year of AZT, hematologic intolerance developed, and AZT was dose-reduced and eventually discontinued. Concomitantly, neuromotor deterioration was again manifest, leading to a total loss of ambulation, hypomimetic facies, and overall rigidity and bradykinesia. Dideoxycytosine (ddC) caused a mild and short-lived neurologic respite. Levodopa (Sinemet, DuPont Merck Pharmaceuticals, Wilmington, DE) was instituted at 7 years 4 months of age, gradually increasing to a dose of 25 mg tid every 4 hours at 8 AM, noon, and 4 PM. This allowed the patient to become much more active and animated, dysarthria lessened, and inde-

pendent ambulation was accomplished. The dosage was maximized to 50 mg of levodopa per dose. At 8.5 years old, the patient continued to deteriorate despite alternative antiretroviral regimens and died at 9 years of age. Over the last 16 months of life, intermittent dystonic spasms developed that responded somewhat to benzodiazepines.

Patient 2 was a 9.5-year-old perinatally HIV-1–infected girl with severe immunodeficiency (absolute CD4 $< 50/\mu l$) initially receiving AZT at a dose of 180 mg/m^2 every 6 hours, with concomitant complications of candidal esophagitis and an HIV-associated nephropathy, who became increasingly and acutely catatonic and nonambulatory with intermittent agitation, elements of rigidity and bradykinesia, urinary incontinence, and swallowing dysfunction. Her clinical diagnosis was "pseudobulbar palsy." CT revealed diffuse "atrophy," and she was diagnosed as PE. Sinemet was started at a dose of 50 mg tid every 4 hours at 8 AM, noon, and 4 PM, which effected a marked and dramatic CNS improvement, characterized by increased alertness, improvement in activity and neuromotor function, enhanced ambulation, better focusing of attention, the ability to respond to questions appropriately, and attempts at talking and singing. Unfortunately, she died 1 month later from unexpected systemic complications not related to the CNS.

Patient 3 was a 4.5-year-old boy with perinatally acquired HIV-1 infection and severe immunodeficiency (absolute CD4 $< 50/\mu l$).[3] At 5 years 9 months, severe stuttering, low voice, and modification of the size of writing was noted. This progressed to expressive language deficit and deterioration of psychometric parameters, and PE was apparent by 7 years of age. At 7 years 9 months, inexpressive facies, stiff posture, and a "shuffling" gait was observed. Additionally, rigidity, akinetism, and pyramidal signs were noted, but without tremor. MRI revealed diffuse "atrophy" but no specific abnormalities within the basal ganglia. Serologic and polymerase chain reaction investigations for opportunistic CNS viral infections were unrevealing (Herpes simplex type 1 and 2, Varicella Zoster, cytomegalovirus, measles, rubella, Epstein-Barr virus, JC virus). Levodopa (Modopar, Roche Company, France) was instituted and progressively increased to 50 mg of levodopa equivalent per dose tid. The patient regained the ability to walk, and facial expression improved. Progressive increases to 100 mg/dose tid caused further improvements, but the 100-mg dose was poorly tolerated. The improvement on levodopa was sustained for 6 months, but the patient succumbed to systemic complications.

Patient 4, a boy with hemophilia A discovered to be HIV-1 infected at 6 years of age secondary to receiving contaminated factor VIII, presented at 10 years of age. Although receiving AZT at a dose of 100 mg/m^2 every 6 hours, with ddC subsequently added, and manifesting severe immunodeficiency (absolute CD4 $< 50/\mu l$), the patient developed a rapidly progressing encephalopathy, the onset characterized by ataxia, but within 2 months manifested a loss of expressive language skills and developed diffuse rigidity with loss of mobility/ambulation and difficulty handling his secretions. Cognition remained intact throughout. An extensive workup investigating infectious, parainfectious, inflammatory, toxic, and metabolic mechanisms did not determine a specific or secondary etiology for the sudden deterioration; MRI revealed only "mild atrophy." Sinemet was started at a dose of 50 mg tid every 4 hours at 8 AM, noon, and 4 PM. Over the next month, he became more animated and interactive, with a concomitant decrease in rigidity and spasticity and an improved ability to clear his secretions. Diminishing effects were noted over the ensuing 3 months, necessitating increases of dosage to 150 mg at 8 AM, 100 mg at noon, and 100 mg at 4 PM. Continued diminishing efficacy was noted 1 year after presentation, and the medication was discontinued with little change in motor function.

Patient 5 was a 13-year-old boy with transfusion-acquired HIV-1 infection, possessing severe immunodeficiency (absolute CD4 $< 100/\mu l$) but otherwise mild systemic complications. Before the discovery of HIV-1 infection, the patient was evaluated for a potential psychiatric syndrome and was administered Stelazine (SmithKline Beecham Pharmaceuticals, Philadelphia, PA). The patient developed a dystonic reaction with a "stiff and shuffling" gait, swallowing difficulties, and excessive drooling. Despite cessation of the drug, the extrapyramidal symptoms persisted, exhibited as rigidity without cogwheeling nor tremor, sustained ankle clonus, postural instability, shuffling gait, and excessive and constant drooling. MRI and CSF examinations were unremarkable. The patient was discovered at this time to be HIV-1 infected. Six months later, Sinemet was started at a dose of 50 mg tid every 4 hours at 8 AM, noon, and 4 PM. This resulted in a cessation of drooling, lessening of rigidity, and marked improvement in gait and postural stability.

Discussion. A subset of children with underlying PE—usually with concomitant severe immunodeficiency and often in the terminal phases of their illness—manifest an extrapyramidal syndrome (EPS) characterized by bradykinesia and hypomimetic/inexpressive facies, rigidity without tremor nor cogwheeling, dysarthria with excessive drooling, postural instability, and loss of ambulatory abilities. Often, the situation is complicated by swallowing dysfunction. Cognition is predominantly preserved, although psychiatric/psychotic symptoms may be manifest (patient 2). In the three children with perinatal HIV-1 infection (patients 1 through 3), an EPS was not manifest until at least 5 years of age and with concomitant severe immunodeficiency. Neuroimaging studies in all patients with PE revealed a nonspecific diminishment of brain parenchymal volume and was devoid of evidence of focal lesions suggesting CNS opportunistic infections. Specific basal ganglia pathology was not evident on neuroimaging studies, although precise volumetric measures of this region were not performed. In one patient (5), the EPS appeared to be a result of a phenothiazine reaction, although it is unclear if his unrecognized HIV-1 infection may have rendered him more susceptible to such a side effect, as can occur in adult patients.[9] The symptoms persisted despite cessation of the phenothiazine and the patient responded well to levodopa therapy.

Institution of 50 mg tid every 4 hours during waking hours of levodopa therapy resulted in improvement in all patients of ambulation, alertness, activ-

ity, and facial expression. Beneficial responses were seen within 2 weeks, but additional gains could be seen after this initial window. An additional benefit was derived from recovery of swallowing function and diminishment of drooling. There was amelioration of symptoms with doses as low as 25 mg and as high as 100 to 150 mg, although these higher doses may not be well tolerated (patient 3). Beneficial effects were sustained for at least 6 months in all surviving patients (patient 2 died after only 1 month of therapy), although some became tolerant of increasing dosages (patient 4). Levodopa therapy in adult patients has not afforded the same degree of clinical success (Berger J, personal communication).

Considering the frequency of basal ganglia pathology identified by previous neuroimaging and neuropathologic studies, it is surprising that there are not more and earlier manifestations of bradykinetic and rigid (EPS) syndromes. Nevertheless, the manifestations of an EPS can greatly affect the HIV-1–infected child's quality of life and requires intervention. Levodopa therapy affords the clinician an important adjunctive therapeutic modality for HIV-1–infected children with extrapyramidal/"parkinsonian-like"/rigid syndromes, allowing improvement in functions of daily living and overall enhancement of the patient's quality of life.

From the Division of Pediatric Neurology (Dr. Mintz), UMDNJ-Robert Wood Johnson Medical School at Camden, and the Children's Regional Hospital, Camden, NJ; the Service de Neurologie (Dr. Tardieu), Dêpartement de Pêdiatrie, Hôpital Bicêtre, France; the Department of Pediatrics (Dr. Hoyt), University of Minnesota Medical School, Minneapolis, MN; the Department of Pediatrics (Drs. McSherry and Oleske), UMDNJ-New Jersey Medical School, and the Children's Hospital of New Jersey, Newark, NJ; and the Department of Pediatrics (Dr. Mendelson), Newark Beth Israel Medical Center, Newark, NJ.

Presented in part at the Neuroscience of HIV Infection: Basic Research and Clinical Frontiers, Paris, France, March 1996.

Received March 25, 1996. Accepted in final form June 10, 1996.

Address correspondence and reprint requests to Dr. M. Mintz, Head, Division of Pediatric Neurology, Cooper Hospital/University Medical School, UMDNJ-Robert Wood Johnson Medical School at Camden, 3 Cooper Plaza, Camden, NJ 08103.

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